

Remote preconditioning and cardiac surgery: regrouping after Remote Ischemic Preconditioning for Heart Surgery (RIPHeart) and Effect of Remote Ischemic Preconditioning on Clinical Outcomes in Patients Undergoing Coronary Artery Bypass Surgery (ERICCA)

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Abstract: Remote ischaemic preconditioning (RIPC) is an attractive cardioprotective strategy. Although results from animal studies and phase II study on humans are convincing, it cannot have a role in clinical practice until benefits in clinical outcomes are proven in phase III study. Two phase III studies were recently published [Remote Ischemic Preconditioning for Heart Surgery (RIPHeart) and Effect of Remote Ischemic Preconditioning on Clinical Outcomes in Patients Undergoing Coronary Artery Bypass Surgery (ERICCA)] and this article discusses their design, results and implications.

Keywords: Remote preconditioning; cardioprotection; cardiac surgery

Submitted Jan 06, 2016. Accepted for publication Jan 20, 2016.

doi: 10.21037/jtd.2016.01.81

View this article at: <http://dx.doi.org/10.21037/jtd.2016.01.81>

Ischaemic heart disease is a major cause of death and disability worldwide and, although percutaneous coronary intervention (PCI) is an effective treatment, many patients still require coronary artery bypass grafting (CABG) procedures. A total of 395,000 CABG procedures were performed in non-federal hospitals in the USA in 2010 (1). Q-wave myocardial infarction (MI) occurs in 4–5% of cases (2) and mortality rates are about 3% at 1 month (3) and 6–8% at 1 year (3,4). Nowadays, patients undergoing CABG tend to be older and there is an increased prevalence of comorbidities such as heart failure and diabetes (5). These factors are associated with adverse outcomes and therefore there is an urgent need for additional cardioprotective strategies. In this regard, remote ischaemic preconditioning (RIPC) has demonstrated much potential, although the results of recent randomised controlled trials have been disappointing.

RIPC is a phenomenon whereby brief episodic ischaemia to an organ or tissue can confer resistance to subsequent

more sustained ischaemic insults in distant organs or tissues. It is underpinned by convincing evidence from studies in animals and in these studies the magnitude of the effect of the intervention is surprisingly large (6). In recent years multiple phase II study have evaluated RIPC in clinical settings but nonetheless progress in confirming a clinical role for RIPC has been slow. Meta-analyses of phase II study in cardiovascular interventions consistently demonstrated cardioprotection when assessed by cardiac enzyme release (7,8) but no consistent effect on clinical outcomes was observed (9). These studies were frequently limited by small sample sizes and heterogeneity in terms of study populations, the RIPC intervention and outcomes (10); hence the need for larger studies was apparent. Until recently no study was adequately powered for clinical endpoints but now two such studies have been published.

The Remote Ischemic Preconditioning for Heart Surgery (RIPHeart) trial was a prospective multicentre double

blinded randomised controlled trial involving 1,403 patients who underwent elective heart surgery with cardiopulmonary bypass and propofol anaesthesia in German institutions (11). The RIPC protocol comprised 4 cycles of 5 min of cuff-induced arm ischaemia with 5 min of reperfusion, and blinding was achieved by using a dummy arm for control group patients. A total of 630 patients underwent isolated CABG surgery and the remainder underwent isolated valve surgery or CABG with valve surgery. The primary outcome was a composite endpoint comprising any of death from any cause, nonfatal MI, new stroke or acute renal failure up to the time of discharge or up to 14 days if hospital stay was in excess of 14 days. A variety of secondary endpoints were also evaluated, including perioperative myocardial injury assessed using serum troponin levels. The trial was initially powered to detect a 33% lower rate of the primary endpoint in the RIPC group compared with the control group (8% *vs.* 12%). However, recruitment was slower than expected and complications were more frequent. After a blinded sample size recalculation the authors estimated that 1,400 patients would be the required sample size. No significant difference was found between the groups regarding the primary outcome or perioperative myocardial injury. Several prespecified subgroup analyses were performed using the primary outcome and no significant effect of RIPC was found. The prespecified subgroups were: isolated CABG surgery, use of cholesterol-lowering drugs, diabetes and EuroSCORE.

The Effect of Remote Ischemic Preconditioning on Clinical Outcomes in Patients Undergoing Coronary Artery Bypass Surgery (ERICCA) trial was a similar trial involving 1,612 patients who underwent CABG with or without valve surgery under cardiopulmonary bypass but without standardised anaesthesia in UK institutions (12). The RIPC protocol was similar to that used in RIPHeart and for the control group blinding was achieved by opening a valve on the blood pressure cuff and thereby preventing its inflation. About 50% of included patients underwent additional valve surgery. The primary outcome was a composite endpoint comprising any of cardiovascular death, nonfatal MI, coronary revascularisation and stroke within 12 months. Serum troponin levels were used to assess perioperative myocardial injury as a secondary outcome. The trial was powered to detect a 27% lower rate of the primary outcome in the RIPC group (14.6% *vs.* 20%). Expected event rates were higher in ERICCA compared with RIPHeart because ERICCA required that participants have a EuroSCORE of 5 or greater, thereby including a higher risk cohort. Similar to RIPHeart, ERICCA

found no difference regarding the primary outcome or perioperative myocardial injury. The primary outcome was also evaluated in a number of prespecified subgroups and again no significant effect was noted. These subgroups were age, EuroSCORE, clamp time, bypass time, left ventricular ejection fraction and diabetes.

Undoubtedly these long-awaited results are disappointing. Given the amount of evidence for RIPC-induced cardioprotection when assessed with biochemical surrogate outcomes in phase II studies, it was hoped that RIPHeart and ERICCA could confirm clinical benefits and bring this simple and cheap intervention one step closer to the bedside. Notwithstanding these recent disappointments, the mechanistic studies on RIPC are convincing and now it is the time to carefully consider the design of future studies. Abandoning RIPC for cardioprotection at this point would be premature. The large number of positive phase II study is unlikely to be related to type 1 error and although RIPHeart and ERICCA have internal validity, the possibility remains that RIPC may offer benefits to a carefully selected population.

In retrospect, one potential issue regarding the design of RIPHeart and ERICCA was the role of propofol anaesthesia. Prior to the commencement of the trials, a report emerged which suggested that propofol abrogated the effect of RIPC (13) and during the course of the trials further evidence to this effect became available from small clinical trials and a meta-analysis (14). Furthermore, a large-scale clinical trial that evaluated RIPC combined with postconditioning in 1,280 patients who underwent cardiac surgery with propofol anaesthesia found no protection with conditioning (15). Unfortunately, prior to the commencement of RIPHeart and ERICCA few data were available on the influence of propofol on RIPC-induced cardioprotection. Notably, RIPHeart required the use of propofol for all patients and although anaesthesia was not standardised in ERICCA over 90% of ERICCA patients received propofol. With the addition of RIPHeart and ERICCA there is now a strong argument for the avoidance of propofol in all future studies. Although this is the obvious path for future research it may have been premature to denounce propofol prior to RIPHeart and ERICCA.

In both RIPHeart and ERICCA, most patients underwent CABG surgery although some had additional valve surgery and some only had valve surgery. It is difficult to see this as a limitation because there have been both positive and negative phase II trials involving CABG and CABG with additional valve surgery (9) and therefore one cannot firmly conclude that RIPC is more effective in one procedure type. RIPC

mitigates ischaemic-reperfusion and theoretically may offer no protection against the additional trauma of valve surgery although conversely RIPC might offer more protection with longer clamp times. Future phase III studies may choose to further limit procedure types in an effort to reduce heterogeneity in the population but this would also slow recruitment and reduce external validity.

Regardless of the slow progress with clinical translation, RIPC remains attractive because it is likely that a subgroup of patients may benefit from RIPC. Although confounders reduce its efficacy and hinder our understanding, the magnitude of its effect in animal studies and the quantity of encouraging proof-of-concept studies in humans should stop us from giving up now.

Acknowledgements

None.

Footnote

Provenance: This is an invited article commissioned by the Section Editor Wenhui Gong (Department of Cardiac Surgery, Ruijin Hospital of Shanghai Jiaotong University, School of Medicine, Shanghai, China).

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Cheung CX, Healy DA, Walsh SR. Remote preconditioning and cardiac surgery: regrouping after Remote Ischemic Preconditioning for Heart Surgery (RIPHeart) and Effect of Remote Ischemic Preconditioning on Clinical Outcomes in Patients Undergoing Coronary Artery Bypass Surgery (ERICCA). *J Thorac Dis* 2016;8(3):E197-E199. doi: 10.21037/jtd.2016.01.81